Na^+/H^+ Exchange Inhibition Improves Long-Term Myocardial Preservation

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Background. Na^+/H^+ exchange plays an important role in the ionic changes observed during myocardial ischemia and reperfusion. We investigated the cardioprotective efficacy of a selective Na^+/H^+ exchange inhibitor, 4-isopropyl-3-methylsulfonyl-benzoylguanidin-methanesulfonate (HOE642), in a canine model of long-term heart preservation.

Methods. Canine donor hearts were stored for 24 hours in hyperkalemic crystalloid cardioplegic solution; in cardioplegic solution enriched with HOE642; in cardioplegic solution enriched with HOE642, with donor and recipient treated with HOE642; in standard cardioplegic solution, with donor and recipient treated with HOE642; or in standard cardioplegic solution, with only the recipient treated. After orthotopic transplantation, pressure-volume relationships were obtained and dogs were weaned from bypass. Morphology was studied.

Results. Myocardial compliance was well preserved when donor and recipient were treated. These groups had the lowest myocardial water content, and no morphologic signs of irreversible damage. In these groups, weaning from cardiopulmonary bypass was successful in 10 of 10 animals, with a cardiac index around 2 $L \cdot min^{-} \cdot m^{-2}$. Only 3 of 5 animals in each of the other three groups could be weaned, with significantly lower cardiac indices.

Conclusions. Treatment with HOE642 in both donor and recipient improves myocardial compliance, post-weaning cardiac index, and ultrastructure of donor hearts preserved for 24 hours and orthotopically transplanted.

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During the past few decades, heart transplantation has become an important option for the treatment of patients with end-stage heart disease. A current report of the International Society for Heart and Lung Transplantation documents that more than 3,000 heart transplantations are performed each year [1]. In this registry, longer cold ischemic preservation time is a significant predictor of 1-year mortality. Therefore, optimization of cardioprotection, specifically for long-term preservation, seems warranted. Extension of the safe ischemic preservation time would allow for better tissue typing and increased organ sharing through longer transports, facilitate logistics, and even prevent some losses of donor organs.

Myocardial ischemia and reperfusion are known to influence cellular ionic transport processes [2]. One such transporter is the Na^+/H^+ exchanger (NHE), which is activated by tissue acidosis and induces intracellular Na^+ overload, consequently causing Ca^{2+} overload through the Na^+/Ca^{2+} exchange system. Ca^{2+} overload causes myocardial contracture, arrhythmia, stunning, and cell necrosis [3]. Myocardial dysfunction may also be induced by edema as a result of the cellular absorption of water caused by the accumulation of end metabolites during ischemia [4]. Myocardial edema or contracture have commonly been observed in long-term preserved hearts [5], and have been shown to cause the loss of ventricular compliance [6], resulting in poor graft function after transplantation.

Inhibition of the NHE system during ischemia and reperfusion prevents or delays myocardial damage by diminishing both Na^+ and Ca^{2+} overload [7, 8]. Na^+/H^+ exchange inhibitors have been widely studied in experimental models of ischemia and reperfusion in vitro [7–16], but not in vivo transplantation models. A new, selective, and more potent NHE inhibitor, 4-isopropyl-3-methylsulfonyl-benzoylguanidin-methanesulfonate (HOE642), has been shown to be tolerated well and to possess favorable kinetic properties, and has been shown to improve postischemic myocardial function in canine donor hearts after orthotopic transplantation from brain-dead and non–brain-dead animals [17]. In that study, less contracture developed after 4 hours of global hypothermic ischemia and significantly superior myocardial compliance was observed during reperfusion when HOE642 was administered [17].

In this study, we tested the hypothesis that NHE inhibition might improve the quality of long-term myocardial preservation. Therefore, we assessed the effect of the NHE inhibitor HOE642 on left ventricular myocardial function, using in vivo pressure-volume measurements of canine donor hearts after 24 hours of cold storage, transplantation, and reperfusion.

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Table 1. Treatment Protocols of the Experimental Groups

Group	CP HOE642	Donor HOE642	Recipient HOE642
1	No	No	No
2	Yes	No	No
3	Yes	Yes	Yes
4	No	Yes	Yes
5	No	No	Yes

CP = cardioplegia.

Material and Methods

Animals

Adult mongrel dogs weighing 22 to 37 kg were used. They received humane care, in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication 85-23, revised 1985) and according to the guidelines of the local ethics committee of the Katholieke Universiteit Leuven.

Dogs were allocated to one of six study groups (Table 1): donor hearts stored in hypothermic standard cardioplegic solution after excision (group 1; n = 6); those stored in cardioplegic solution enriched with HOE642 (0.4 mg/L; group 2; n = 6); those stored in cardioplegic solution enriched with HOE642, with donor and recipient treated with HOE642 (2 mg · kg^{-1}; group 3; n = 6); those stored in standard cardioplegic solution, with donor and recipient treated with HOE642 (group 4; n = 6); and hearts stored in standard cardioplegic solution, with only the recipient treated with HOE642 (group 5; n = 6). Nonischemic normal hearts were classified as group C (n = 6).

The dogs were premedicated by intramuscular injection of 5 mg · kg^{-1} piritramide (Dipidolor), and were anesthetized by intravenous administration of 20 to 25 mg · kg^{-1} sodium pentobarbital (Neumbutal). After endotracheal intubation, artificial ventilation was instituted and adapted to keep arterial blood gasses and pH within the physiologic range.

Preservation of Donor Hearts

After median sternotomy, heparin (300 IU · kg^{-1}) was administered intravenously, the superior vena cava was closed, and the inferior vena cava was divided. Some groups of donor dogs received HOE642, 2 mg · kg^{-1}, intravenously 15 minutes before the start of ischemia. One liter of hypothermic (2° to 4°C) cardioplegic solution [17] was infused at a pressure of 150 mm Hg in the aortic root after aortic cross-clamping. Afterwards, the heart was excised and immersed in cold cardioplegic solution.

Tilting disc prostheses (Björk-Shiley monostrut #17 and #23; Prangins, Switzerland) were implanted in both the aortic and mitral position during the immersion period. If necessary, an aortoplasty with a Dacron patch to widen the aortic root was performed. Myocardial temperature was continuously monitored by a thermistor probe in the interventricular septum. The explanted heart was then stored for 24 hours in a plastic bag containing hypothermic cardioplegic solution, and kept in an isothermal box containing crushed ice with myocardial temperature monitored.

Orthotopic Heart Transplantation

The recipient dogs were selected with a difference in body weight between the recipient and donor dogs of less than 5 kg. After general anesthesia, pancuronium bromide (Pavulon; Organon, West Orange, NJ), 0.1 mg · kg^{-1}, and piritramide, 1 mg · kg^{-1}, also were administered. Esophageal and rectal temperatures were monitored throughout the entire procedure.

A catheter in the right brachial artery was used to monitor arterial blood pressure, while central venous pressure was monitored through the right brachiocephalic vein. The heart was exposed by a median sternotomy and a pulmonary arterial thermistor catheter was inserted into the main pulmonary artery.

After administration of heparin (300 IU · kg^{-1}) and methyl prednisolone (5 mg · kg^{-1}), both femoral arteries were cannulated to provide arterial inflow for the extracorporeal circulation. The azygos vein was ligated. The superior vena cava and inferior vena cava were cannulated separately for venous drainage to the cardiopulmonary bypass (CPB) system.

Standard CPB was carried out using a system made up of a centrifugal pump (Bio-Medicus; Bio-Medicus, Inc, Eden Prairie, MN), two roller pumps (Sarns Cardiovascular Equipment; Sarns Inc, Ann Arbor, MI), a membrane oxygenator (Univox Membrane Oxygenation System; Baxter Healthcare Corporation, Bentley Laboratories Division, Irvine, CA) with a venous reservoir (Minimax 1316 Filtered Hardshell Reservoir; Medtronic Cardiopulmonary, Anaheim, CA), and a heat exchanger (Blanketrol; Cincinnati Subzero Products, Inc, Cincinnati, OH). Priming of the CPB system was performed using Plasma-lyte A (Baxter, Lessines, Belgium), 500 mL, Geloplasma (Institut Mérieux Benelux, Brussels, Belgium), 500 mL, and dog blood, 400 mL, obtained from the donor dog. Pump blood flow was maintained at 2.4 L · min · m^{-2} and gas flow between 3 and 4 L · min^{-1} during CPB. After cooling to a rectal temperature of 25°C, the donor heart was transplanted orthotopically using a conventional method with topical cooling using ice slush.

In those groups where the recipient was treated with HOE642, a dose of 2 mg · kg^{-1} was given to the recipient animal intravenously 15 minutes before the start of reperfusion of the transplanted heart. The transplanted heart was reperfused for 60 minutes with decompression of the left ventricle. The heart was defibrillated electrically when the myocardial temperature was greater than 31°C if the heart did not spontaneously defibrillate. During the reperfusion period, the heart was paced at 110 beats · min^{-1}

At the end of reperfusion functional measurements of left ventricular performance were carried out and transmural myocardial biopsies were taken from the anterior wall of the transplanted heart for histologic examination.

Morphologic Examination

The transmural biopsy specimens taken at the end of reperfusion were immediately fixed with 2% glutaraldehyde in Sorensen's buffer, pH 7.4. After 24 hours of fixation, the tissue samples were sliced and postfixed by immersion in 1% OsO_4 and 2% pyroantimonate for Ca^{2+} staining. The tissues were then dehydrated and embedded in epoxy. Specimens were stained with toluidine blue and 50-nm sections were mounted on copper grids and stained with uranyl acetate and lead citrate. Tissue ultrastructure was assessed under a transmission electron microscope (Philips CM10) in a blinded fashion to determine the severity of cell injury. The cell injuries were scored from − to +++ as none = 0, occasional and mild = ±, mild = +, moderate = ++, and severe = +++.

Measurement of Left Ventricular Function

Isovolumetric pressure-volume relationships were constructed to determine left ventricular function. A latex balloon with a 7-F Millar Milkro-Tip Catheter Pressure Transducer (Millar Instruments, Inc, Houston, TX) inside was inserted into the left ventricle through the apex. A venting catheter (16F) was also placed outside the balloon in the left ventricular cavity and right atrial blood was drained by gravity after total CPB. The volume of the ventricle was then increased in increments from 5 mL to 35 mL by inflation of the balloon. Balloon herniation through the aortic or mitral valves was prevented by the two implanted valvular prostheses.

Hemodynamic Measurement After Weaning From Cardiopulmonary Bypass

In all groups, weaning from CPB was carried out with positive inotropic support (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ each of both dopamine and dobutamine). The hemodynamic changes (heart rate, systolic and diastolic arterial pressure, central venous pressure, left atrial pressure, and pulmonary arterial pressure) were continuously recorded. Cardiac output was measured using the thermodilution technique, and the mean of triplicate measurements obtained with a Cardiac Output Computer, COM-1 (American Edwards Laboratories, Irvine, CA) was calculated.

Measurement of Heart Weight

At the end of the experiment, the transplanted heart was explanted and the left ventricular free wall was weighed to obtain wet weight. The specimen was then frozen at −30°C and dried under vacuum for 48 hours to obtain the dry weight.

Data Analysis

MYOCARDIAL WATER CONTENT. Myocardial water content (MWC) was calculated using the following formula: MWC = (1 − dry to wet weight ratio) · 100%.

LEFT VENTRICULAR COMPLIANCE BEFORE WEANING FROM CARDIOPULMONARY BYPASS. Left ventricular compliance was calculated from the end-diastolic pressure-volume relationship measured using the intraventricular balloon during CPB. To correct for hearts of different sizes, left ventricular volume data were normalized to a heart weight of 100 g [18]. A second-order polynomial curve was fitted to the relationship generated by plotting the normalized volume against end-diastolic pressure with commercially available software (Delta Graph Pro 3.0; DeltaPoint, Inc., Monterey, CA) using the following equations [17]: $P_{ed} = a \cdot (V_{ed} - b)^2$ and $a = dP \cdot dV^{-1} \cdot 2 \cdot (V_{ed} = b)^{-1}$, where P_{ed} is end-diastolic pressure, a is an index of ventricular stiffness, V_{ed} is normalized end-diastolic volume, and b is the volume at zero pressure [17]. This equation includes a zero value for P_{ed} (for $V_{ed} = b$), but excludes negative values and pressure values on normalized volume less than 10 mL [19, 20].

LEFT VENTRICULAR SYSTOLIC PERFORMANCE BEFORE WEANING FROM CARDIOPULMONARY BYPASS. This was studied using the relationship between the normalized volume and peak developed pressure. Peak developed pressure and volumes were obtained by calculating and plotting the difference between peak systolic-pressure and the end-diastolic pressure-volume relationship. A linear function with two parameters was fitted to this plot using the following equation: $P_{PDP} = aV + b$, where P_{PDP} is peak developed pressure, a is the slope of the linear developed pressure-volume relationship as an indicator of left ventricular performance, and b is the developed pressure in the left ventricle at zero volume [17].

POSTWEANING MYOCARDIAL PERFORMANCE. This was assessed by the measurement of the cardiac index after weaning from CPB. Cardiac index was calculated as cardiac output divided by body surface area ($L \cdot min^{-1} \cdot m^{-2}$), where the body surface area was calculated as 0.04 + 0.2 × body weight.

Statistical Analysis

All data are expressed as absolute numbers or means ± standard error. Multiple group comparisons were performed by analysis of variance (factorial or repeated measures). For post-hoc testing, Fisher's protected least significant difference test was used. Statistical analysis was performed with StatView 4.0.1 statistical software (Abacus Concepts, Inc, Berkeley, CA) and Statistica 4.5 (Statsoft, Tulso, CA) and a probability level of less than 0.05 was considered significant.

Results

Myocardial Temperatures

After cross-clamping of the ascending aorta in donor animals, myocardial temperature decreased to ±10°C during the first 1 or 2 minutes of cardioplegic solution infusion and decreased gradually afterwards. Within 4 hours of preservation in the isothermal box with ice, myocardial temperature was ±1.3°C until the end of the 24-hour preservation period.

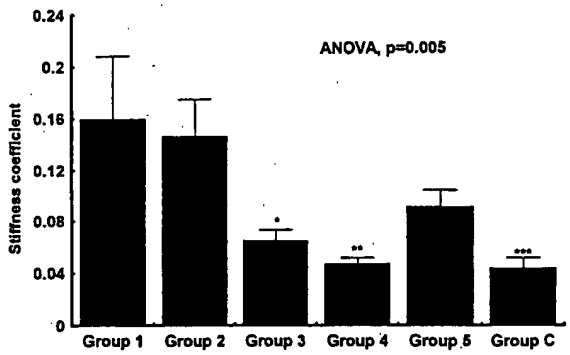

*Fig 1. The stiffness coefficient a, as described in the methodology section, is shown in the five groups of preserved hearts, and in the nonischemic control group for comparison. Means are shown with standard error of the mean as error bars. (ANOVA = analysis of variance; *p = 0.010 versus group 1 and p = 0.025 versus group 2; **p = 0.003 versus group 1 and p = 0.007 versus group 2; ***p = 0.002 versus group 1 and p = 0.006 versus group 2.)*

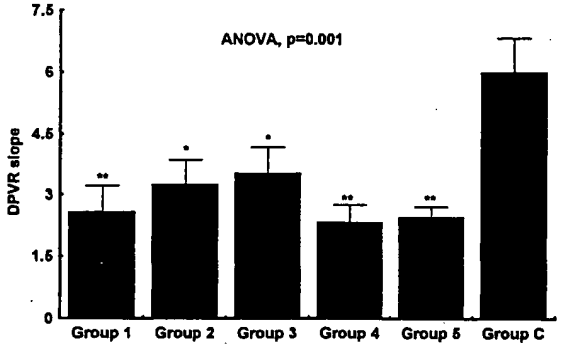

*Fig 2. The slope of the developed pressure-volume relationship (DPVR) is shown for the study groups. Means are shown with standard error of the mean as error bars. (ANOVA = analysis of variance; *p < 0.01 versus group C; **p < 0.001 versus group C.)*

Myocardial Compliance

The stiffness coefficient a as described in the Material and Methods section, differed significantly between the groups ($p = 0.005$) by analysis of variance (Fig 1). The hearts preserved for 24 hours in standard hypothermic cardioplegia, group 1, showed a significantly higher stiffness coefficient than the nonischemic normal hearts, group C (0.160 ± 0.049 versus 0.044 ± 0.008; $p = 0.002$), thus long-term hypothermic storage in hypothermic cardioplegia decreases myocardial compliance.

Groups 1 and 2 showed the lowest compliance (the highest stiffness coefficients, 0.160 ± 0.049 and 0.146 ± 0.029, respectively). The mean stiffness coefficient for groups 3, 4, and C were 0.065 ± 0.008, 0.047 ± 0.0046, and 0.044 ± 0.008, respectively. Group 5, with a mean stiffness coefficient of 0.082 ± 0.017, exhibited intermediate compliance. There was no significant difference in the stiffness coefficient between groups 1 and 2. Group 4 had the lowest stiffness coefficient, and this was statistically different from that of groups 1 ($p = 0.003$) and group 2 ($p = 0.007$). Hearts from group 3 were not found to be significantly different from those of group 4 or group C, but were significantly more compliant than hearts from groups 1 ($p = 0.010$) and 2 ($p = 0.025$). The stiffness coefficient from hearts in group 5 showed no significant difference when compared with hearts from the other groups.

Myocardial Performance

Myocardial performance was analyzed using developed pressure-volume relationships and the cardiac index assessed after weaning from CPB.

DEVELOPED PRESSURE-VOLUME RELATIONSHIPS. Left ventricular performance after transplantation using CPB without any inotropic support differed significantly between the experimental groups ($p = 0.001$ by analysis of variance) (Fig 2). The steepest slope in the relation was observed for the nonischemic control group. This control group was highly significantly different from all other experimental groups. However, there were no significant differences in the developed pressure-volume relationship slope between the preserved donor heart groups.

POSTWEANING CARDIAC WORK PERFORMANCE. After 60 minutes of reperfusion and construction of pressure-volume relationships, the dogs were weaned from CPB with low doses of inotropic support. Serial determinations of cardiac index were performed every 10 minutes for 1 hour. All animals in groups 3 and 4 could be weaned from CPB. They showed a recovery of cardiac index to 1.99 ± 0.16 and 2.72 ± 0.22 $L \cdot min^{-1} \cdot m^{-2}$, respectively. Only 3 of 5 experimental animals could be weaned from CPB in groups 1, 2, and 5. The cardiac index of the weaned animals was always less than 1.5 $L \cdot min^{-1} \cdot m^{-2}$. At 60 minutes after weaning from CPB, the cardiac indices of groups 3 and 4 were significantly different from those of group 1 (0.627 ± 0.28 $L \cdot min^{-1} \cdot m^{2}$; $p < 0.0001$), group 2 (0.78 ± 0.34 $L \cdot min^{-1} \cdot m^{-2}$; $p < 0.001$), and group 5 (0.669 ± 0.34 $L \cdot min^{-1} \cdot m^{2}$; $p < 0.0001$). No difference was found between groups 3 and 4, and no difference was found between groups 1, 2, and 5 (Fig 3).

Myocardial Water Content

The myocardial water content in the left ventricular myocardial samples differed significantly between the groups (group 1: 81.17 ± 0.58; group 2: 80.65 ± 1.06; group 3: 77.76 ± 1.47; group 4: 76.58 ± 1.74; group 5: 80.23 ± 0.35; and group C: 75.91 ± 0.80; $p = 0.008$ by analysis of variance). The myocardial water content was significantly lower in nonischemic control hearts and in group 4, compared with that in groups 1, 2, and 5 (all pairwise comparisons, $p < 0.05$). Group 3 differed significantly only from group 1 ($p = 0.038$). Comparisons of myocardial water content between groups 3, 4, and C revealed no significant differences, nor did comparisons between groups 1, 2, and 5.

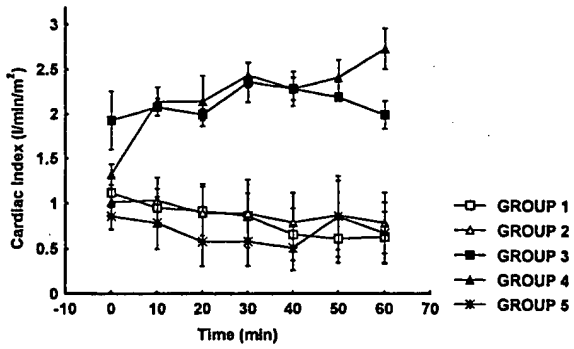

Fig 3. Cardiac index after weaning from cardiopulmonary bypass for the five study groups. Cardiac index was significantly lower in groups 1, 2, and 5 than in groups 3 and 4 (all $p < 0.001$). Means are shown with standard error of the mean as error bars.

Ultrastructure

Extensive interstitial and intracellular edema was seen in hearts from groups 1 and 2. This was less pronounced in hearts from group 5, and was only slight in hearts from groups 3 and 4 (Table 2, Fig 4).

Hearts from groups 3, 4, and 5 showed no mitochondrial calcium clumps, but these were present in the majority of mitochondria in group 1, indicative of severe, irreversible injury. Some calcium clumps were seen in group 2. Mitochondrial swelling, structural degeneration of the cristae, and rupture was present in groups 1 and 5, and was evident to a lesser degree in group 2. Only mild mitochondrial swelling was seen in groups 3 and 4. Taking the degree of calcium precipitation and swelling together gives us the mitochondrial injury score, as presented in Table 2. The glycogen deposits were slightly diminished in groups 3 and 4, and were more severely diminished in groups 1, 2, and 5.

Comment

Improving the quality of myocardial preservation might extend the safe ischemic preservation period, with its logistic and tissue-typing advantages. On the other hand, it might improve the quality of routinely transplanted hearts undergoing ischemia and reperfusion. Recently, Myers and Karmazyn [16] reported improved cardiac function using the in vitro isolated reperfused heart model after 12-hour hypothermic storage and administration of the NHE inhibitor HOE694. In an earlier study [17], our group showed that HOE642 significantly improved myocardial compliance in an in vivo model of heart transplantation in dogs after 4 hours of donor heart preservation. These results prompted us to investigate the myocardial protective efficacy of NHE inhibition on myocardial function and ultrastructure of canine donor hearts transplanted after 24 hours of hypothermic storage. We found that HOE642 significantly improves compliance, and significantly improves the weaning potential and postweaning cardiac index if both donor and recipient are treated. We found no proven effect of adding the drug to the cardioplegic solution. It is clearly not sufficient to treat the recipient only.

Table 2. Degrees of Ultrastructural Injuries in the Six Groups

Variable	C	1	2	3	4	5
Edema	−	+++	+++	+	±	++
Mitochondrial injury	−	+++	++	+	+	++
Glycogen deposits	+++	±	+	++	++	±

C = control.

For our functional measurements, two mechanical valve prostheses were implanted to prevent balloon herniation during the measurement of pressure-volume relationships. We employed this preventive step because previous studies in which this method was used to determine pressure volume relationships were inaccurate because of balloon herniation during the procedure.

The stiffness coefficient differed significantly between the groups studied (Fig 1). However, we could not find significant differences in myocardial performance between the groups after long-term heart preservation when the slope of the developed pressure-volume relationship was analyzed (Fig 2), indicating that the beneficial effect of NHE inhibition influences myocardial compliance to a greater extent than pressure development.

Only the groups in which the donor and recipient, or the donor, recipient, and preserved heart, were treated with HOE642 showed significantly better myocardial compliance than the untreated group. Moreover, in neither of these groups was there any evidence of damage to mitochondrial structures (Fig 4). In addition, all animals could be weaned from CPB using minimal dosages of positive inotropic agents, with acceptable cardiac indices (Fig 3). Supplementation of the cardioplegic solution with HOE642 did not significantly improve myocardial preservation, as no significant differences were found in compliance, isovolumetric pressure development, or postweaning cardiac index between groups 1 and 2, nor between groups 3 and 4. In group 5, where the donors were not treated with HOE642, the mean compliance was halfway between the fully treated group 3 and the untreated group 1. In a recent in vitro study using isolated perfused rabbit hearts after 12 hours of cold preservation, a significant cardioprotective effect was observed when an NHE inhibitor was used only during reperfusion [16]. In that study, addition of the NHE inhibitor to the cardioplegic solution did not confer additional benefit. Pretreatment of the donor, however, was not tested in that model; this could possibly produce even better results, because in our study treatment of both the ischemic and reperfusion phases produced a higher compliance and better protection against ultrastructural damage than treatment during the reperfusion phase only. Treatment of the recipient and donor also produced completely successful weaning from CPB. From our study, it is clear that NHE inhibition during both the ischemic and reperfu-

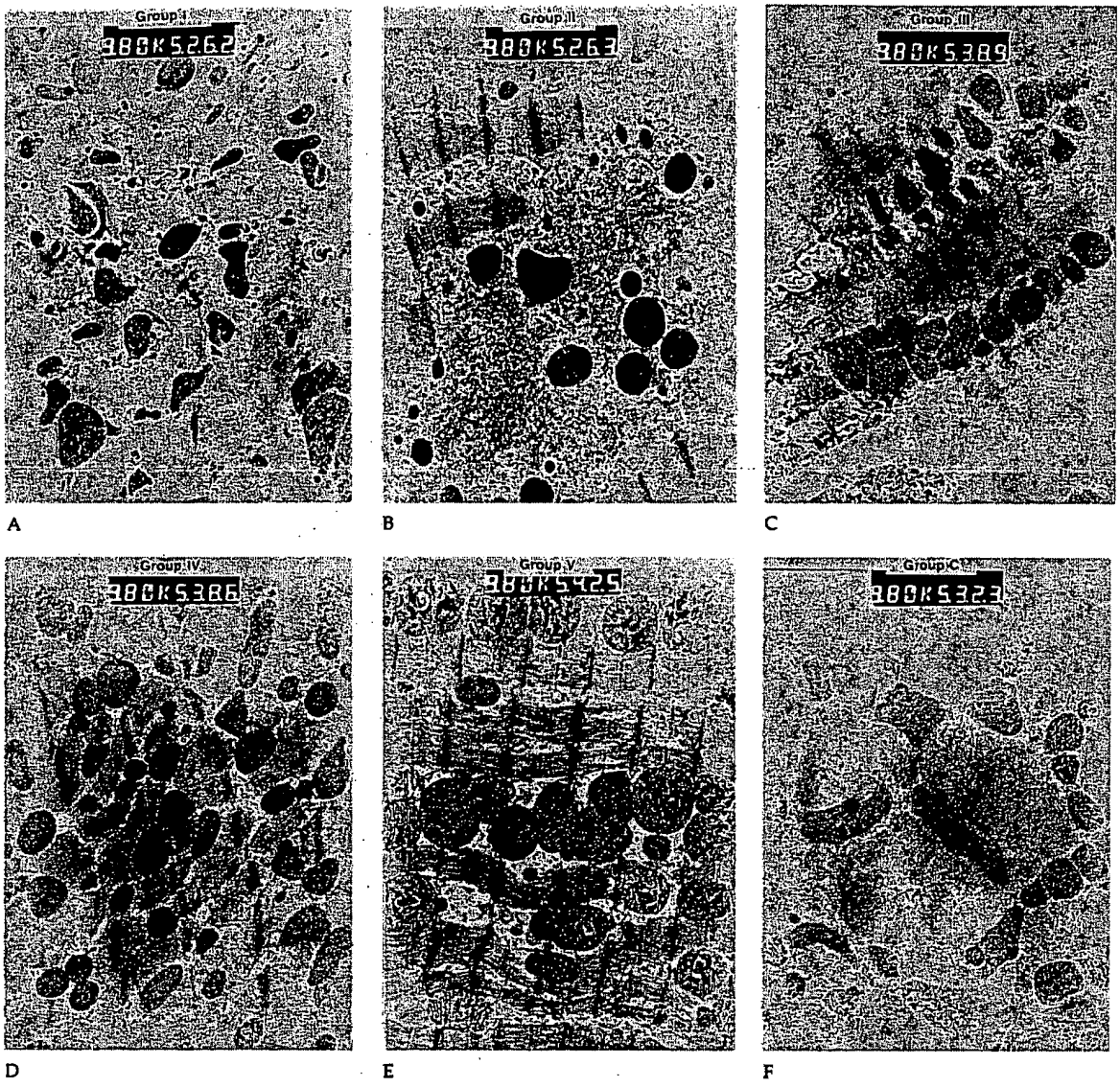

Fig 4. Ultrastructural pictures of a representative example from each group are shown. (A) Group 1: intercellular and intracellular edema and mitochondrial structural injuries eg, calcium clumps and ruptured or swollen mitochondria. (B) Group 2: mild degree of intercellular edema and no calcium clumps in mitochondria. (C) Group 3: well-preserved mitochondrial structures and no intercellular or intracellular edema. (D) Group 4: well-preserved mitochondrial structures and no intercellular or intracellular edema. (E) Group 5: prominent intercellular or intracellular edema formation. (F) Group C: normal ultrastructure.

sion phases is necessary for optimal cardioprotective effects.

An older study by Spray and colleagues [21] demonstrated edema of the intercellular space and markedly diminished or absent glycogen content of transplanted canine hearts after 24-hour preservation in an oxygenated hypothermic intercellular solution. In the study presented here, ultrastructure was maintained with relatively well-preserved glycogen, with only slight intercellular edema formation in the hearts in which the NHE inhibitor was administered in both donor and recipient. When the donor heart was arrested and stored in cold cardioplegic solution enriched with HOE642, myocardial edema was evident and similar to that in donor hearts arrested and stored in cardioplegic solution alone. Although hearts from group 2 showed markedly fewer signs of irreversible myocardial damage when compared with the untreated controls, this was not directly reflected in superior hemodynamic recovery. These morphologic findings, together with the protection seen in

the isolated reperfused rabbit heart model when an NHE inhibitor only was added to the cardioplegic solution [16], together with the absence of any detrimental effect of the addition of HOE642 to the cardioplegic solution, suggest that complete treatment of donor, recipient, and cardioplegic solution might be optimal.

In conclusion, HOE642, when used to treat both donor and recipient, markedly improves myocardial compliance, postweaning cardiac index, and ultrastructure of canine donor hearts hypothermically preserved for 24 hours. Our data suggest that this inhibitor may extend the maximal clinically acceptable ischemic preservation time presently allowed for donor hearts.

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